

EXHIBIT 4



General Approach to Pain Management

ASK:

Always ask patient about the presence of pain and accept the patient's report of pain.

ASSESS:

Perform a comprehensive pain assessment:

- Onset, duration, and location
- Quality (sharp, dull, diffuse, throbbing, etc)
- Intensity (1-10 scale, for example)
- Aggravating and alleviating factors
- Effect on function and quality of life
- Patient's goal for pain control
- Response to prior tx if condition is chronic
- History and physical examination

TREAT:

- With older adults, start dose low, go slow, but go!
- Avoid IM route, the PO route is preferred
- Treat persistent pain with regularly scheduled meds
- Two drugs of the same class (eg, NSAIDs) should not generally be given concurrently, however long- and short-acting opioids may be prescribed together
- Avoid meperidine (per American Pain Society and ISMP) and propoxyphene (cardiotoxic and i efficacy)

MONITOR:

- Assess and reassess pain frequently
- Most opioid agonists have no analgesic ceiling dose; titrate to relief and assess for adverse effects
- Assess, anticipate, and manage opioid adverse effects aggressively
- Discuss goals and plans with patient and family
- Addiction rarely occurs unless there is a hx of abuse
- Watch for red flags of addiction:
 - 1) Compulsive use
 - 2) Loss of control
 - 3) Use despite harm

Breakthrough Pain Management

General

- Use **long-acting** opioids around the clock for **baseline** management of persistent pain
- Use **short-acting** opioids PRN (rescue) for **breakthrough** pain
- Consider using the same drug for both baseline and rescue doses whenever possible (eg long-acting morphine + short-acting morphine)

Rescue Dosing

- The rescue dose is 10%-15% of the 24-h total daily dosage
- Oral rescue doses should be available every 1-2 h; parenteral doses every 15-30 minutes

Adjustment

- If the patient is consistently taking ≥ 3 rescue doses daily, consider increasing the baseline round-the-clock dosage
- Recalculate rescue dose whenever the baseline dosage is changed

Example

Calculate rescue dose for patient on baseline coverage of MS Contin 200 mg q 12 h:

1. Calculate total daily dosage:
 $200 \text{ mg} \times 2 = 400 \text{ mg morphine/d}$
2. Establish rescue dose:
 $10\%-15\% \text{ of } 400 \text{ mg} = 40-60 \text{ mg short-acting morphine}$
3. Oral rescue dose therefore is:
 $\text{morphine } 40-60 \text{ mg PO q } 1-2 \text{ h}$
4. Parenteral rescue dose (based on continuous infusion): Calculate based on 25%-50% of hourly dose

Pain Types

Type	Examples	Quality
Somatic pain	Trauma, burns, bone metastasis	Constant, sometimes throbbing or aching, tender, and localized to the site of origin
Visceral pain	Renal stone passage, small bowel obstruction, appendicitis, cancer	Poorly localized, may be referred to distant cutaneous site (eg, diaphragmatic irritation referred to ipsilateral shoulder), often associated with nausea or diaphoresis
Neuropathic pain	Nerve compression, cancer invasion of neural structures, diabetic neuropathy, postherpetic neuropathy, trigeminal neuralgia	Prolonged, severe, burning, lancinating, squeezing, hypersensitivity to pain; possible tachycardia, diaphoresis; tends to be resistant to opioids and difficult to treat

Interventional Pain Management Techniques

Technique	Indications
Lumbar epidural steroid injection (ESI)	Inflammation associated with conditions such as spinal stenosis, disc herniation or degenerative disc disease
Facet block	Diagnostic tool used to isolate and confirm the specific source of back pain (facet joints)
Selective nerve root block (SNRB)	Primarily used to diagnose the specific source of nerve root pain and, secondarily, for therapeutic purposes such as treatment for a far lateral disc herniation
Neurolytic blocks (chemical radiofrequency ablation)	Good for localized pain not requiring multiple segmental blocks; successful SNRBs should be done prior to neurolysis

Severe-Intractable Pain:

1. Strong (intrathecal/intraspinal opioids [+/- adjuvant])
2. Invasive procedures (nerve block, myelotomy, nerve/spinal stimulation, intraventricular opioids), or intrathecal ziconotide if 1 ineffective

Moderate-Severe Pain:

1. Weak PO opioids/opioid combination drugs → Strong PO/IV opioids if 1 ineffective; consider using adjuvants, especially for neuropathic pain

Mild-Moderate Pain:

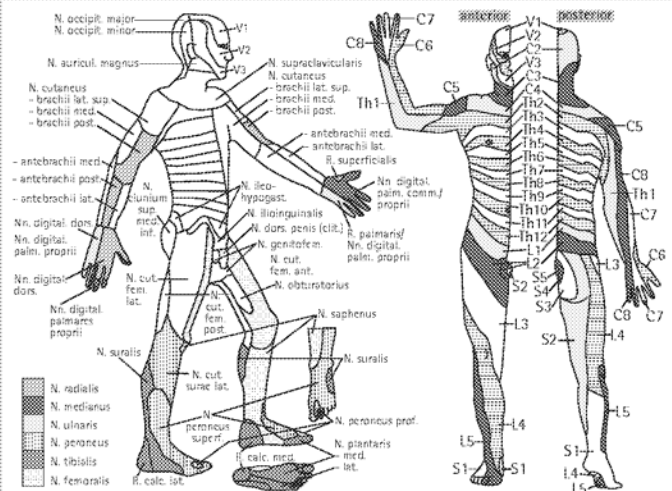
1. Nonopioid analgesics → 2. Weak PO opioids/opioid combination drugs, if 1 ineffective

Mild Pain: Nonopioid analgesics

Terminology of Pain Management

Term	Definition	Term	Definition
Allodynia	Feeling nonpainful stimulation as painful	Hyperpathia	Reduced sensation
Analgesia	No pain	Hypoesthesia	Decreased cutaneous stimulation
Anesthesia	No sensation	Paresthesia	Abnormal sensation without stimulus
Anesthesia dolorosa	Pain in an area with no stimulation	Hyperesthesia	Increased response to mild stimuli
Hypoalgesia	Diminished response to pain	Dysesthesia	Unpleasant sensation with or without stimulation

Innervation and Dermatome Map



Local Anesthetics

Drug	Onset	Duration (h)	CNS Tox	Heart Tox	Pot ¹	Comments
Amides						Slow, hepatic metabolism; high systemic toxicity potential, but low allergic potential; bupivacaine has high cardiotoxic potential; prilocaine is associated with methemoglobinemia at high doses
Lidocaine	fast	1-2	++	+	4	
Bupivacaine	slow	3-6	+++	+++++	16	
Mepivacaine	mod	1-3	++	+	3-4	
Prilocaine	fast	2-3	+	+/-	3-4	
Ropivacaine	mod	Epidural ~7 PNB ² 2-6	++(+)	+++	16	
Esters						Rapid metabolism by plasma cholinesterase; high allergic potential (PABA derivatives); tetracaine is the most toxic among the esters
Procaine	fast	0.5-1	+	+	1	
Chlorprocaine	fast	0.5-1	+	+	4	
Tetracaine	slow	1.5-3	+++	+++	16	

¹Pot = Potency; ²PNB = Peripheral nerve block

Opioid Equianalgesic Dosing

Drug	Dose	Equivalent	Half-life	Duration	Opioid-switching example
Morphine	30 mg	10 mg	2-3 h	2-4 h	Switch morphine 30 mg PO q4h to PO hydromorphone: 1. Calc 24-h morphine dose: $30 \text{ mg} \times 24\text{h}/4\text{h} = 180 \text{ mg/d}$ 2. Locate PO equivalency: $7.5 \text{ mg hydromorphone} = 30 \text{ mg morphine}$ 3. Calc hydromorphone total daily dosage: $= 180 \times 7.5/30 = 45 \text{ mg/d}$ 4. Calculate individual dose: $45 \text{ mg} / 6 = 7.5 \text{ mg q4h}$ 5. Reduce dose by 25%-50% to account for incomplete cross-tolerance, then titrate up prn: 3.75-5.63 mg q4h
Morphine CR (KDS Contin)	30 mg	10 mg	2-3 h	8-12 h	
Oxycodone	20 mg	-	2-3 h	3-4 h	
Oxycodone CR	20 mg	-	2-3 h	8-12 h	
Hydrocodone	30 mg	-	4 h	3-4 h	
Hydromorphone	7.5 mg	1.5 mg	2-3 h	2-4 h	
Methadone	Acute 20mg Chronic 2-4 mg	Acute 10mg Chronic 2-4 mg	12-100 h	4-12 h	
Fentanyl	-	0.1 mg	3-4 h	4-6 h	
Fentanyl transmucosal duragesic patch	-	-	16-24 h	48-72 h	

Opioid Patient-Controlled Analgesia (PCA) Regimens

Drug	Conc. (mg/mL)	Bolus dose (mg)	Lockout interval (min)	Hourly max (mg)
Morphine	1	0.5-2.5	5-15	5-15
Fentanyl	0.025 or 0.050	0.0125-0.050	5-10	0.1-0.3
Hydromorphone	1	0.3	5-15	1.25-3

These dosages are for opioid-naïve patients; much larger dosages may be needed for opioid-tolerant patients

Weak Opioids and Combination Drugs

Drug	Dose	Adverse Effects	Comments
Codeine	15-120 mg PO/IM/SC q 4-6 h	Drowsiness, constipation, bradycardia, euphoria, confusion, pruritus	Requires dosage reduction in renal failure
Tramadol	25-50 mg q 4-6 h Max 400 mg/d, 300 mg/d in elderly	Headache, confusion, sedation	Dual-action opioid agonist, norepi/serotonin receptor antagonist; ↓ seizure threshold
Hydrocodone + acetaminophen	1 tab (2.5-10 mg / 325-750 mg) PO q 4-6 h prn	Sedation, respiratory depression, hypotension, pruritus, confusion, constipation	Max 4 g/day acetaminophen
Oxycodone + acetaminophen	1 tab (2.5-10mg / 300-650 mg) PO q 4-6 h prn	Similar opioid effects	Max 4 g/day acetaminophen

Nonopioid Analgesics

Drug	Dosage	Adverse Effects	Comments
NSAIDs			
Aspirin	500-1000 mg q4-6h Max 4 g/d	GI bleeding, ↓ platelet adhesiveness, renal toxicity	Caution in hepatic/renal disease
Choline magnesium trisilicate (Trilisate)	500 mg initial then 250 mg q 6-8 h Max 1500 mg/d	Lower incidence of GI effects	Caution in hepatic/renal disease; does not inhibit platelet aggregation
Ibuprofen	200-400 mg q 4-6 h Max 2400 mg/d	GI bleeding, ↓ platelet adhesiveness, renal toxicity	Caution in hepatic/renal disease
Naproxen	500 mg initial then 250 mg q 6-8 h Max 1500 mg/d	GI bleeding, ↓ platelet adhesiveness, renal toxicity	Caution in hepatic/renal disease
Nabumetone	500-750 mg q8-12h Max 2 g/d	GI bleeding, ↓ platelet adhesiveness, renal toxicity	Caution in hepatic/renal disease
Ketorolac	30 mg IV initial, then 15-30 mg q 6 h Max 150 mg/d day 1, then 120 mg/d	GI bleeding, ↓ platelet adhesiveness, renal toxicity	In elderly 30 mg IV initial, then 15-30 mg thereafter. Use restricted to max 5 days. Caution in hepatic/renal disease
Celecoxib	100-200 mg q 12 h Max 200-400 mg/d	Lower incidence of GI effects	Does not inhibit platelet aggregation
Other			
Acetaminophen	500-1000 mg q4-6h Max 4 g/d, 3 g/d if liver dis or elderly	Liver toxicity at high doses	Use caution in the elderly and individuals with hepatic disease
Ziconotide	Intrathecal init ≤2.4 µg/d; titrate by ≤2.4 µg/d q2-3 times/prn to max 19.2 µg/d prn	Neurologic and cognitive impairment, dizziness, confusion, memory deficits, N/V/D, ↑ CK	N-type Ca channel blocker; for intractable pain unresponsive to other agents

Analgesic Adjuncts¹

Drug	Dose	Adverse Effects	Comments
Antidepressants²			
Amitriptyline	Init 25 mg PO qhs Increase to 100 mg PO qhs prn	Sedation, constipation, urinary retention, tachycardia, conduction abnormalities, seizures	Tricyclic antidepressant (TCA); has the most anticholinergic effects
Desipramine	100 mg PO qd	similar effects	TCA; fewer adverse effects
Imipramine	100 mg PO qd	similar effects	TCA
Nortriptyline	50–100 mg PO qhs	similar effects	TCA; less sedating
Duloxetine	60 mg PO qd Max 120 mg/d	Sedation, insomnia, dizziness, nausea	SNRI; indicated for diabetic neuropathic pain

Anticonvulsants

Carbamazepine	Init 100 mg PO bid Titrate to max of 1,600 mg/d div qid	Nausea, vomiting, diarrhea, hyponatremia, rash, pruritus, drowsiness, blurred vision, headache, dizziness, Stevens-Johnson syndrome	Indicated for trigeminal or glossopharyngeal neuralgia; requires CBC and LFT monitoring; Asians with the HLA-B*1502 allele are predisposed to Stevens-Johnson
Gabapentin	Day 1: 300mg PO qhs Day 2: 300 mg PO bid Day 3: 300 mg PO tid Max 1,800 mg/d PO div tid	Somnolence, dizziness, ataxia	Indicated for postherpetic neuralgia; requires dose reduction in renal failure
Pregabalin	Init 50 mg PO tid Max 100 mg PO tid	Weight gain, somnolence, dizziness, ataxia, peripheral edema	Indicated for postherpetic neuralgia, diabetics neuropathic pain, fibromyalgia; requires dose reduction in renal failure

Other Agents

Capsaicin cream	0.025%–0.075%	Itching, stinging, erythema	Apply 3–5/d x2–4 wk
Lidocaine 5% patch	Up to 3 patches at once for up to 12 h within 24 h period	Local skin reactions such as blisters or erythema	Indicated for postherpetic neuralgia
Clonidine	Epidural infusion as opiate adjunct: init 0.5 µg/kg/h; 1 dose to effect	Drowsiness, dizziness, dry mouth, constipation, skin reactions, orthostatic hypotension	Opiate adjunct for severe, intractable pain, unresp to other analgesics or spinal opiates alone, esp neuropathic pain

¹May be used alone or in combination with opioids, often in the treatment of neuropathic pain.

²With the exception of duloxetine, use of these agents in pain management is off-label, however, they are considered by pain specialists as first-line treatment in diabetic peripheral neuropathy pain (DPNP).

Anticoagulation in Neuraxial Anesthesia

Drug	Minimum Elapsed Time*	Drug	Minimum Elapsed Time*
ASA/NSAIDs	No risk	IV Heparin	Delay for 1 h after needle placement; remove indwelling catheters 2–4 h after last dose
Clopidogrel	7 days	Abciximab	48 h
Warfarin	4–5 days	Eptifibatide	8 h
Ticlopidine	14 days	LMWH	10–12 h (low dose); 24 h (high dose)
SubQ Heparin	No risk	Thrombolytics	Avoiding regional block is recommended

*Minimum elapsed time between the last drug dose and administration of anesthesia.

Management of Opioid Adverse Events

Adverse Event	Management
Constipation	Begin bowel regimen when opioid therapy is initiated. Include a mild stimulant laxative (eg, Senna, Cascara) + stool softener (eg, Colace) at bedtime or in divided doses as routine prophylaxis.
Sedation	Tolerance typically develops. Hold sedatives/anxiolytics, reduce opioid dose. Consider stimulants such as caffeine, methylphenidate, or dextroamphetamine.
Nausea/vomiting	Dosage reduction, opioid rotation. Consider transdermal scopolamine patch, metoclopramide, or prochlorperazine.
Pruritus	Caused by opioid induction of histamine release that is inversely correlated to potency (morphine > fentanyl). Management involves dosage reduction, opioid rotation, and possible use of an antihistamine (eg, diphenhydramine).
Hallucinations	Dosage reduction, opioid rotation. Consider neuroleptics (eg, haloperidol, risperidone)
Confusion/delirium	Dosage reduction, opioid rotation, neuroleptic therapy (eg, haloperidol, risperidone)
Myoclonic jerking	Dosage reduction, opioid rotation. Consider clonazepam, baclofen.
Respiratory depression	Sedation precedes respiratory depression. Stop opioid! Give low-dose naloxone - dilute 0.4 mg (1 mL of a 0.4 mg/mL amp of naloxone) in 9 mL of normal saline (NS) for final concentration of 0.04 mg/mL.

Recommendations for Treatment of Diabetic Peripheral Neuropathy Pain (DPNP)

1st-tier drugs	Duloxetine, oxycodone CR, pregabalin, tricyclic antidepressant (TCA) class drugs
2nd-tier drugs	Carbamazepine, gabapentin, lamotrigine, tramadol, venlafaxine
Honorable mention drugs	Topical capsaicin, topical lidocaine, bupropion, citalopram, paroxetine, phenytoin, topiramate, methadone

Adapted from the Mayo Clinic 2006 Consensus Guidelines for the treatment of DPNP.